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# Refined Composite Multivariate Multiscale Entropy based on Variance for Analysis of Resting-state Magnetoencephalograms in Alzheimer's Disease

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**Abstract**— Alzheimer's disease (AD) is one of the fastest growing neurological diseases. Multiscale entropy with coarse-graining based on mean ( $MSE_\mu$ ) has been widely used to characterize AD. Alternatively, multiscale entropy based on variance ( $MSE_\sigma^2$ ) has been recently proposed to quantify the dynamics of volatility (variance) of univariate signals. Here, we extend the  $MSE_\sigma^2$  to multivariate signals to take into account both the time and spatial domains for discrimination of resting-state magnetoencephalogram (MEG) recordings of 36 AD patients from those of 26 normal controls. We also consider the usefulness of the refined composite  $mvMSE_\sigma^2$  ( $RCmvMSE_\sigma^2$ ) to understand if the  $RCmvMSE_\sigma^2$  can better discriminate AD group from control subjects in comparison with  $mvMSE_\sigma^2$ . The results show  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$ , unlike exiting multiscale-based methods, lead to significant differences between control and AD patients at all scale factors. The results obtained by the  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$  are similar. Thus, refined composite technique might not enhance the detection of different pathological states, especially when signals are not too noisy and short. Finally, our findings show that the  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$  can be useful tools for the analysis of real signals to characterize different kinds of dynamics.

**Keywords**— Alzheimer's disease; refined composite multivariate multiscale entropy; complexity; statistical moments.

## I. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in elderly people affecting intellectual, behavioural and functional abilities [1-3]. As AD progresses, there exist changes in the dynamical brain activity that can be recorded in magnetoencephalogram (MEG) and electroencephalogram (EEG) time series [4-7]. Since EEG and MEG signals are nonlinear, nonlinear techniques have been widely used to detect these changes [4, 5, 8].

One of the most powerful nonlinear approaches to quantify the irregularity or uncertainty of a time series is entropy [9, 10]. Sample entropy (SampEn) is a prevalent technique showing the negative natural logarithm of the conditional probability that a signal of length  $N$ , having repeated itself within a tolerance  $r$  for  $m$  sample points, will also repeat for  $m+1$  sample points [9].

In spite of the SampEn popularity, it is estimated only at a single time scale and thus, may fail to consider the multiple temporal scales underlying nonlinear dynamics [11]. To this end, multiscale entropy whose coarse-graining process uses mean ( $MSE_\mu$ ) was introduced [11]. In the  $MSE_\mu$  algorithm, the original signal is first divided into non-overlapping segments of length  $\beta$ , named scale factor. Afterwards, the average of each segment is estimated to obtain the coarse-grained signals. Finally, the SampEn value is calculated for each coarse-grained signal [11].

However, the MSE-based approaches are not able to take into account the dynamics across channels of a multichannel (multivariate) recording. For such signals, evaluation of cross-statistical properties between multiple channels is needed for a complete understanding of their underlying dynamics [12, 13]. In this sense, multivariate SampEn ( $mvSE$ ) and subsequently, multivariate  $MSE_\mu$  ( $mvMSE_\mu$ ) as the combination of the coarse-graining process and  $mvSE$ , were proposed [13].

$MSE_\sigma^2$  whose coarse-graining process uses variance ( $MSE_\sigma^2$ ) has been recently introduced to take into account the dynamics of the volatility (variance) of a signal over multiple time scales to extract dynamical properties of spread [14]. It was shown that the dynamics of the volatility of heartbeat recordings obtained from healthy young subjects is highly complex. It was also demonstrated that the multiscale complexity of the volatility, not only the multiscale complexity of the mean heart rate, degrades with aging and pathology.

Linear and nonlinear irregularity and complexity EEG analyses have been employed to understand physiological processes in both healthy and pathological conditions in AD [1, 7, 15-18]. The studies showed that control subjects' EEG and MEG signals are more complex than AD patients' recordings [1, 7, 15-18].

In this study, to take into account both the spatial and time domains, we first propose multivariate  $MSE_{\sigma^2}$  ( $mvMSE_{\sigma^2}$ ) as an extension of  $MSE_{\sigma^2}$  for multichannel signals. Inasmuch as the refined composite technique increased the stability and reliability of multivariate entropy-based result for short and/or noisy signals [19], we propose refined composite  $mvMSE_{\sigma^2}$  ( $RCmvMSE_{\sigma^2}$ ) to understand if the refined composite approach can highlight differences between AD patients and control subjects compared with  $mvMSE_{\sigma^2}$ .

## II. MATERIALS

### A. Subject Groups

This dataset includes 62 subjects (36 AD patients and 26 control subjects). All subjects gave their informed consent for the study, which was approved by the local ethics committee. Diagnoses were confirmed with thorough tests. To screen the cognitive status, the mini-mental state examination (MMSE) was utilized [5].

The 36 AD subjects (24 women; age =  $74.06 \pm 6.95$  years, mean  $\pm$  standard deviation, SD; MMSE score =  $18.06 \pm 3.36$ , mean  $\pm$  SD) met the criteria for probable AD based on the guidelines of the NINCDS-ADRDA [20].

The control participants included 26 subjects (17 women; age =  $71.77 \pm 6.38$  years; MMSE score =  $28.88 \pm 1.18$ , mean  $\pm$  SD). The difference in age between two groups was not significant ( $p$ -value = 0.1911, Student's  $t$ -test).

### B. MEG Data

Resting state MEG time series were obtained with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) in a magnetically shielded room at the MEG Centre Dr. Pérez-Modrego (Spain). All 62 subjects were eyes closed and laid on a hospital bed in a relaxed state. They were requested to avoid falling asleep and not to move eyes and head. For each subject, five minutes of MEG resting state activity were recorded at a sampling frequency of 169.54Hz. The time series were divided into segments of 10s (1695 samples per channel) and visually inspected by the use of an automated thresholding process to discard segments noticeably contaminated with artefacts [5]. The impact of cardiac artefact was decreased from the signals using a constraint blind source separation procedure [21] to avoid bias in the computation of multivariate approaches. Finally, a bandpass FIR filter with cut-off frequencies 1.5Hz and 40Hz was used to the data.

## III. (REFINED COMPOSITE) MULTIVARIATE MULTISCALE ENTROPY BASED ON VARIANCE

Both the  $mvMSE_{\sigma^2}$  and  $RCmvMSE_{\sigma^2}$  methods include two main steps: I) coarse-graining process and II) calculation of mvSE at each scale factor.

*I. Coarse-graining process:* Assume we have a  $p$ -channel ( $p$ -variate) time series  $\mathbf{Y} = \{y_{q,b}\}_{b=1}^C$ ,  $q=1, \dots, p$ , where  $C$  is the length of each channel's signal. As an extension of  $MSE_{\sigma^2}$  [14] to multi-channel signals, we use variance in the coarse-graining process as follows:

$$\sigma^2 x_{q,i}^{(\beta)} = \frac{1}{\beta} \sum_{b=(i-1)\beta+1}^{i\beta} (y_{q,b} - \mu x_{q,i}^{(\beta)})^2, \quad 1 \leq i \leq \left\lfloor \frac{C}{\beta} \right\rfloor = N, \quad 1 \leq q \leq p \quad (1)$$

where  $\beta$  is the time scale factor and

$$\mu x_{q,i}^{(\beta)} = \frac{1}{\beta} \sum_{b=(i-1)\beta+1}^{i\beta} y_{q,b}, \quad 1 \leq i \leq \left\lfloor \frac{C}{\beta} \right\rfloor = N, \quad 1 \leq q \leq p. \quad \text{For}$$

smaller number of time sample points in the coarse-grained sequence, the coarse-graining process may yield unstable or undefined entropy values [19]. To tackle this shortcoming, we proposed the refined composite technique for multi-channel time series extending the previous definition for univariate time series [19, 22]. The first step of refined composite multivariate multiscale entropy-based approaches is generating  $\beta$  coarse-grained multivariate time series  $z_{\alpha}^{(\beta)} = \{x_{\alpha,q,i}^{(\beta)}\}$   $1 \leq \alpha \leq \beta$  where

$$\sigma^2 x_{\alpha,q,i}^{(\beta)} = \frac{1}{\beta} \sum_{b=(i-1)\beta+\alpha}^{i\beta+\alpha-1} (y_{q,b} - \mu x_{\alpha,q,i}^{(\beta)})^2, \quad 1 \leq i \leq \left\lfloor \frac{C}{\beta} \right\rfloor = N, \quad 1 \leq q \leq p, \quad 1 \leq \alpha \leq \beta \quad (2)$$

As can be seen in Fig. 2 in [19], in  $RCmvMSE_{\sigma^2}/RCmvMFE_{\sigma^2}$ , for each scale factor  $\beta$ , we have  $\beta$  different multivariate signals  $\mathbf{Z}_{\alpha}^{(\beta)}$ , while in the  $mvMSE_{\mu}$  and  $mvMSE_{\sigma^2}$  methods, only  $\mathbf{Z}_1^{(\beta)}$  is considered. The second step of multivariate multiscale techniques is calculating multivariate sample entropy for each scale factor.

*II) calculation of mvSE at each scale factor:* For a defined scale factor  $\beta$ , the mvSE of the coarse-grained signal is calculated [13, 23]. To calculate the mvSE, multivariate embedded vectors are initially generated [13]. In [24], the Takens embedding theorem for multivariate concept is described. Using the  $p$ -channel signal  $\mathbf{X} = \{x_{q,i}\}_{q=1, i=1}^{q=p, i=N}$  where  $N$  is the length of each coarse-

grained time series  $\{\mathbf{x}_q\}_{q=1}^p$ , the multivariate embedded reconstruction is defined as:

$$X_m(i) = [x_{1,i}, x_{1,i+\tau_1}, \dots, x_{1,i+(m_1-1)\tau_1}, x_{2,i}, x_{2,i+\tau_2}, \dots, x_{2,i+(m_2-1)\tau_2}, \dots, x_{p,i}, x_{p,i+\tau_p}, \dots, x_{p,i+(m_p-1)\tau_p}] \quad (3)$$

where  $\mathbf{m}=[m_1, m_2, \dots, m_p]$  and  $\boldsymbol{\tau}=[\tau_1, \tau_2, \dots, \tau_p]$  are the embedding and the time lag vectors, respectively.

For  $p$ -variate time series  $\{\mathbf{x}_q\}_{q=1}^p$ , the mvSE algorithm, as a natural extension of standard SampEn, is described as follows [13]:

1. Form multivariate embedded vectors  $X_m(i) \in R^m$  where  $i=1, 2, \dots, N-n$  and  $n = \max\{\mathbf{m}\} \times \max\{\boldsymbol{\tau}\}$ .
2. Calculate the distance between any two composite delay vectors  $X_m(i)$  and  $X_m(j)$  as the maximum norm.
3. For a given  $X_m(i)$  and a threshold  $r$ , count the number of instances  $P_i$  where  $d[X_m(i), X_m(j)] \leq r, i \neq j$ . Next, calculate the frequency of occurrence as  $\phi_i^m(r) = \frac{1}{N-n} P_i$  and define a global quantity  $\phi^m(r) = \frac{1}{N-n} \sum_{i=1}^{N-n} \phi_i^m(r)$ .
4. Extend the dimensionality of the multivariate delay vector in (3) from  $m$  to  $(m+1)$  (while keeping the dimension of the other variables unchanged).
5. Repeat steps 1 to 4 and find  $\phi_i^{(m_q+1)}(r)$ . Next, calculate  $\phi_i^{(m+1)}(r)$  which denotes the average over all  $n$  of  $\phi_i^{(m_q+1)}(r)$ . Finally, find  $\phi^{(m+1)}(r)$  which stands for the average over all  $i$  of  $\phi_i(r)$  in an  $(m+1)$ -dimensional space.
6. Finally, mvSE is defined as:

$$mvSE(\mathbf{X}, \mathbf{m}, \boldsymbol{\tau}, r) = -\ln \left( \frac{\phi^{(m+1)}(r)}{\phi^m(r)} \right) \quad (4)$$

As noted before, based on the proposed refined composite technique [19], for each scale factor  $\beta$ , we have  $\beta$  different multivariate time series  $\mathbf{Z}_\alpha^{(\beta)}$ . For each of  $\mathbf{Z}_\alpha^{(\beta)}$ ,  $\phi_{\beta,\alpha}^m | (\alpha=1, \dots, \beta)$  and  $\phi_{\beta,\alpha}^{m+1} | (\alpha=1, \dots, \beta)$  are separately calculated. Then, the average of values of  $\bar{\phi}_{\beta,\alpha}^m$  and  $\bar{\phi}_{\beta,\alpha}^{m+1}$  on  $1 \leq \alpha \leq \beta$  are computed. Finally, the RCmvMSE is computed as follows:

$$RCmvSE(X, \lambda, m, r) = -\ln \left( \frac{\bar{\phi}_{\beta,\alpha}^{m+1}}{\bar{\phi}_{\beta,\alpha}^m} \right) \quad (5)$$

$m_k$ ,  $\tau_k$ , and  $r$  for all of the approaches were respectively chosen 2, 1, and 0.15 multiplied by the SD of the original

time series according to [9, 13]. It is worth noting that the number of sample points is at least  $10^m$ , or preferably at least  $30^m$ , to robustly estimate mvSE, according to [13, 25]. Note that the codes used in this paper are publicly-available at <http://dx.doi.org/10.7488/ds/1432>.

#### IV. RESULTS AND DISCUSSION

To assess the usefulness of  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$  to characterize AD, MEG signals in terms of regions, according to Fig. 1, five scalp areas (anterior, left and right lateral, central, and posterior) were defined. Both the  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$  approaches were used for channels 31, 32, 48, 49, 51, 52, 69, 70 (anterior region), 15, 17, 19, 21, 23, 25, 27, 29 (central region), 53, 55, 57, 96, 100, 114, 116, 118 (left lateral region), 64, 66, 68, 107, 111, 125, 127, 129 (right lateral region), 39, 41, 59, 62, 102, 105, 120 and 123 (posterior region) with a maximum of time scale factor  $\beta=10$  [13, 19].

The results obtained by  $mvMSE_\sigma^2$ ,  $RCmvMSE_\sigma^2$ , and  $mvMSE_\mu$  [26] are respectively shown in Fig. 2, Fig. 3, and Fig. 4. At all scale factors, the average of the  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$ , unlike  $mvMSE_\mu$ , values of AD patients are lower than those of controls. This is in agreement with this fact that AD patients' signals are less complex than controls' time series [6, 27] and shows a superior performance of  $RCmvMSE_\sigma^2$  and  $mvMSE_\sigma^2$  over  $mvMSE_\mu$  in the ability to reveal a decrease in complexity due to AD.

A Student's  $t$ -test was also used to evaluate the differences in the metrics between AD subjects and controls. We adjusted the false discovery rate independently for each multivariate entropy method. Those scales having the adjusted  $p$ -values smaller than 0.05, named significant, are depicted with \* in Fig. 2 to 4. The adjusted  $p$ -values show that  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$ , unlike  $mvMSE_\mu$ , achieve significant differences at all scale factors. This fact shows an advantage of  $mvMSE_\sigma^2$  and  $RCmvMSE_\sigma^2$  in comparison with  $mvMSE_\mu$ . This supports the usefulness of variance-based multivariate multiscale entropy over mean-based one to discriminate AD subjects from controls.

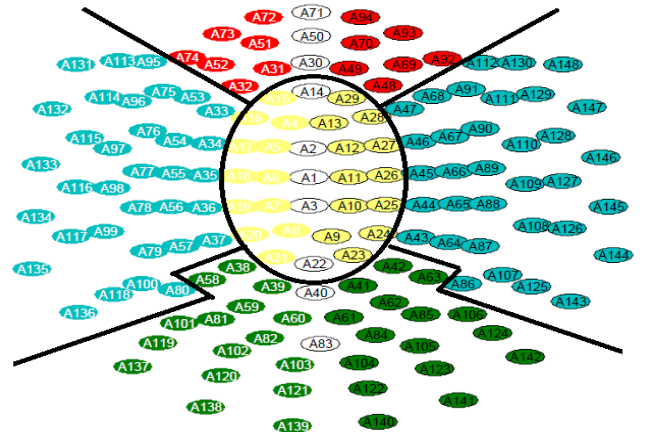


Fig. 1. Distributions of the MEG sensors into anterior (red), central (yellow), left lateral (blue with white text), right lateral (blue with black text), and posterior (green) hemispheres. The midline sensors are marked in white.

In [19], it was demonstrated that, for noisy and short signals, the refined composite technique can decrease the standard deviation of the results leading to smaller adjusted  $p$ -values. Our findings also show the adjusted  $p$ -values obtained by  $\text{mvMSE}_{\sigma^2}$  and  $\text{RCmvMSE}_{\sigma^2}$  show similar differences and, therefore, the refined composite technique is not needed for the data in this case. This is in agreement with this fact that when time series are not too noisy or short, the refined composite technique may not enhance the detection of different pathological states [19].

An important problem in multivariate entropy-based methods is having a large number of channels, especially for long signals, since simultaneously considering all the channels takes long time. Accordingly, we picked up a subset of channels (8 channels) for each region. In the future, we try to tackle this problem based on the similarity or dissimilarity concepts, such as mutual information.

## V. CONCLUSIONS

We have proposed two variance-based multivariate multiscale entropy, namely  $\text{mvMSE}_{\sigma^2}$  and  $\text{RCmvMSE}_{\sigma^2}$  to quantify the dynamics of volatility of multivariate signals. Then, we inspected the usefulness of these methods to characterize resting-state MEG signals for discrimination of AD patients from control subjects. The results have shown similar behaviour of  $\text{mvMSE}_{\sigma^2}$  and  $\text{RCmvMSE}_{\sigma^2}$  but both of techniques had better performance to characterize AD than  $\text{mvMSE}_{\mu}$ . All in all, we conclude that the variance-based multivariate entropy methods offer complexity profiles for analysis of physiologic and non-physiologic time series.

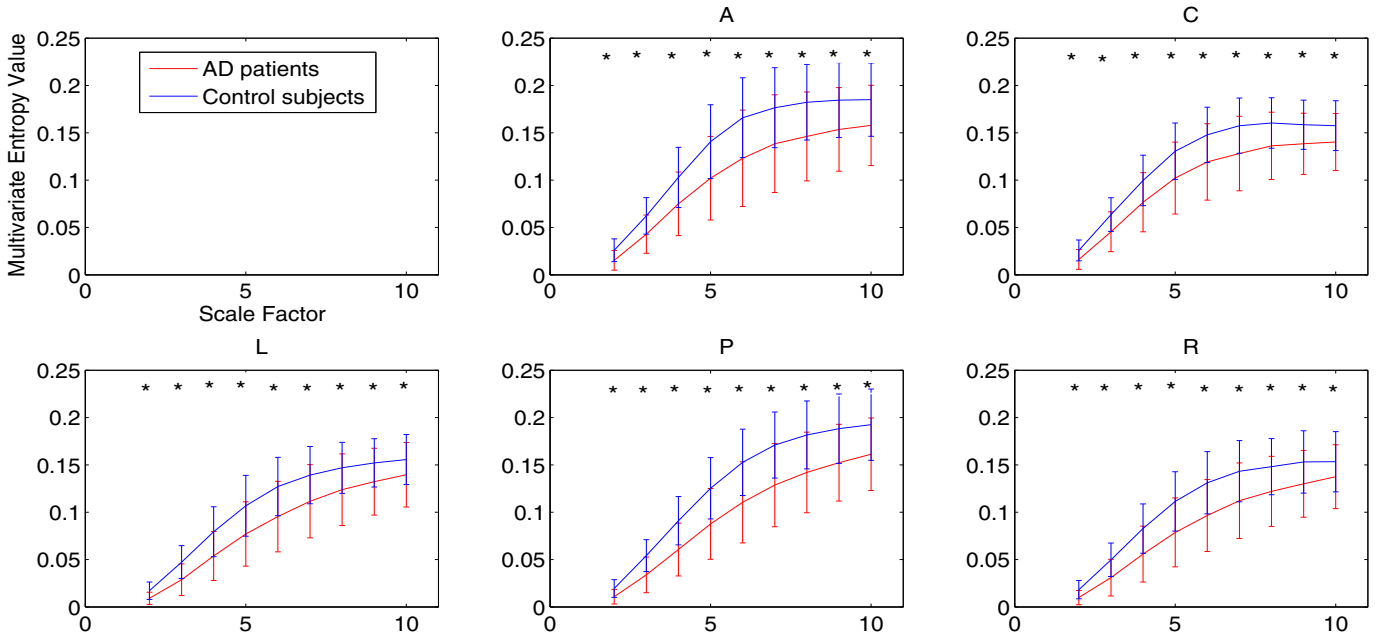


Fig. 2. Average values for  $\text{mvMSE}_{\sigma^2}$  over 10 scale factors for AD (red) and controls (blue) in each scalp region: anterior (A), central (C), right lateral (R), left lateral (L), and posterior (P). Bars indicate standard deviation. Asterisks indicate scales with significant differences between groups.

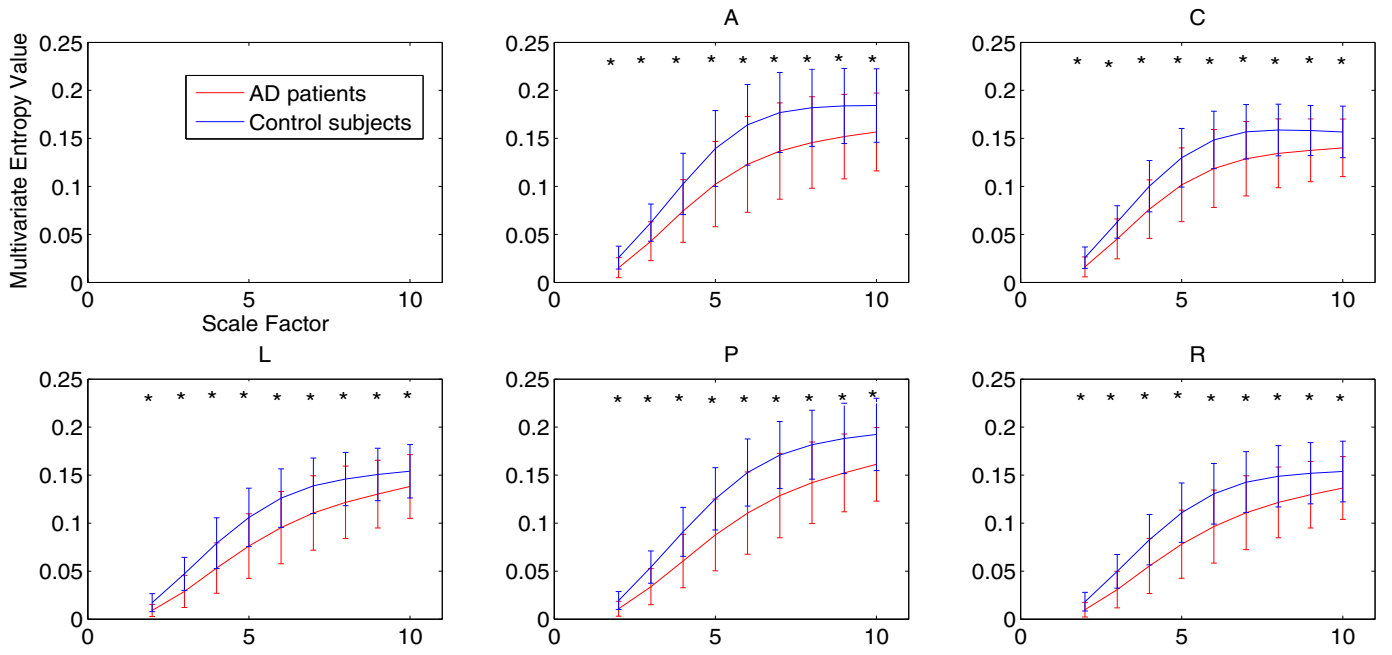


Fig. 3. Average values for  $RCmvMSE_{\sigma^2}$  (b) over 10 scale factors for AD (red) and control groups (blue) for 5 scalp regions, described in Fig. 2.

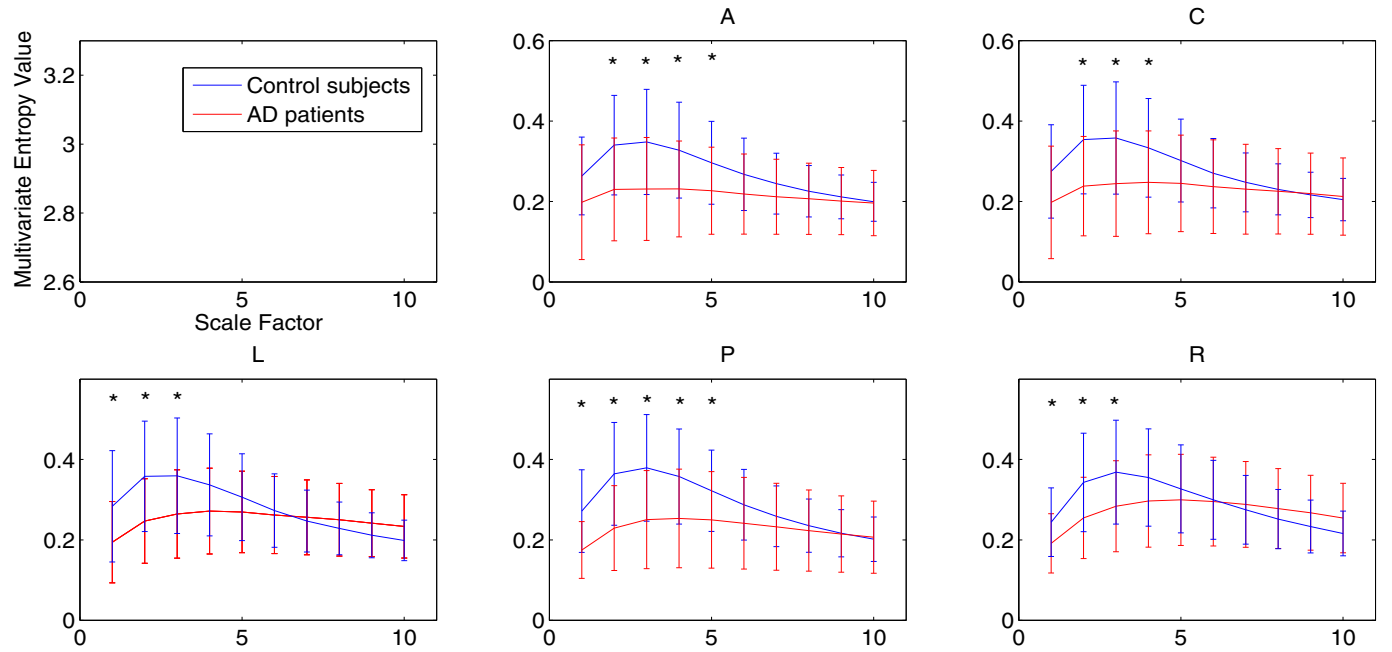


Fig. 4. Average values for  $mvMSE_{\mu}$  (b) over 10 scale factors for AD (red) and control groups (blue) for 5 scalp regions, described in Fig. 2.

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